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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YOUNG, JOSEPHINE	
ART UNIT	PAPER NUMBER
1623	7

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/014,472	KERN ET AL.	
	Examiner	Art Unit	
	Josephine Young	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) *9 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in Paper No. 6, dated December 19, 2002, is acknowledged. The traversal is on the ground(s) that it would not be a serious burden to examine Group I with Group II. This is not found persuasive because these inventions are distinct and have acquired a separate status in the art as shown by their different classification and their recognized divergent subject matter. A reference for one group could not reasonably be expected to be a reference for the other. Further, searching both of the inventions constitutes a burdensome search, as a thorough search comprises a search of foreign patents and non-patent literature, as well as the appropriate U.S. patent classifications. To search the two independent and distinct inventions, set forth supra, would indeed impose an undue burden upon the examiner in charge of this application.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 9-10 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Objections

Claim 1 is objected to because of the following informalities: The Markush grouping for the matrix metalloproteinases is not in conventional form. As such, it can be construed as ambiguous, in that it is unclear if the proper grouping should be

interpreted as at least one matrix metalloproteinase selected from the group consisting of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1 and gelatinase A (MMP-2).

Further, claim 3 is objected to because the disorder "inflammatory" is not grammatically correct.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 1-8 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the inhibition of certain matrix metalloproteinases, does not reasonably provide enablement for treating the wide breadth of disorders conceivably embraced by the claims, and in particular, does not reasonably provide enablement for *preventing* any disorder. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which disorders would be effected by inhibiting certain matrix metalloproteinases for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as no assay was described with respect to any particular disorder, out of the numerous disorders that could conceivably be effected by modification of the activity of at least one matrix metalloproteinase. Further, undue experimentation is required to determine the efficacy of a prophylactic treatment with enoxaparin for which the instant invention is applicable, as no molecular or animal model is widely accepted to predict for such. There has not been provided adequate guidance in the written description or in the prior art for accomplishing such.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, while certain agents and compositions are known to treat certain forms of inflammation, no effective agent or composition has been

found for the treatment of all types of tissue/joint disorders. Further, there are no agents that are known to prevent any tissue/joint disorder. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compounds/compositions needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there are some working examples of the inhibition of certain matrix metalloproteinases, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-8 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "disorder ... wherein the disorder displays enhanced activity ..." in claim 1 renders the claims in which it appears indefinite. In the absence of a specific disorder or distinct language to ascertain which disorders exhibit the requisite enhanced activity, the identity of said disorder would be difficult to describe and the metes and bounds of said method of treating or preventing a disorder, which displays enhanced

activity, that Applicant regards as the invention cannot be sufficiently determined because they have not been particularly pointed out or distinctly articulated in the claims.

The term "enhanced activity" in claim 1 is a relative term that renders the claim indefinite. The term "enhanced activity" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-8 are rejected under 35 U.S.C. 103(a) as being unpatentable over International Publication No. WO 92/19249 A1 to YEDA RESEARCH AND DEVELOPMENT CO. LTD (YEDA) in view of WO 00/56283 A1 to THE B.F.GOODRICH COMPANY (B.F.GOODRICH).

Applicant claims methods to treat disorders that display enhanced activity of at least one matrix metalloproteinase selected from the group consisting of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1 and gelatinase A (MMP-2), using enoxaparin. Applicant claims numerous disorders in particular, including degenerative joint disorder, connective tissue disorder, wound healing disturbance, periodontal disorder, disorder of the locomotor system, disturbance of bone metabolism, osteoarthritis, inflammation, immunological or metabolism-related acute and chronic arthritis. Finally, Applicant claims various modes of administration and dosage ranges.

YEDA teaches that low molecular weight heparin (LMWH) differ from heparin in that they show improved antithrombotic performance as well as double the half-life and higher bioavailability. See page 10, lines 5-14. Further, YEDA teaches on page 10, lines 15-19, that low molecular weight heparin administered at sub-anticoagulant doses are effective in the prevention and/or treatment of pathological processes involving induction of TNF-α. On page 3, lines 13-25, YEDA teaches that induction of TNF-α in turn enhances collagenase in the skin and causes the breakdown of bone and cartilage, is involved in the pathogenesis of many undesirable inflammatory conditions, autoimmune disease, graft rejection, vasculitis and atherosclerosis. In particular, on page 11, lines 27-34, YEDA discloses that a commercially available low molecular weight heparin is Lovenox or enoxaparin. On page 8, lines 1-6, YEDA discloses preferred modes of administration and in claims 14-17 discloses preferred dosage ranges.

YEDA does not specifically teach that the disorders that display enhanced activity of TNF-α would also display enhanced activity of at least one matrix metalloproteinase

selected from the group consisting of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1 and gelatinase A (MMP-2).

B.F.GOODRICH discloses that matrix metalloproteinases (MMPs) are metal-binding proteinases secreted by connective tissue cells, inflammatory phagocytes and transformed cells. See page 1, lines 7-8. On page 4, lines 4-10, B.F.GOODRICH teaches that MMPs play a significant role in many pathological conditions including cancer, heart disease, wound healing and degradation of articular cartilage matrix such as osteoarthritis. Further, B.F.GOODRICH teaches certain polymer compositions that are effective inhibitors of MMPs. On page 24, lines 4-7, B.F.GOODRICH discloses that such compositions can contain heparin.

It would have been obvious to one of ordinary skill in the art to use the low molecular weight heparins of YEDA to treat disorders that display enhanced activity of at least one matrix metalloproteinase selected from the group consisting of neutrophil collagenase (MMP-8), aggrecanase, hADAMTS1 and gelatinase A (MMP-2), since the disorders that display enhanced activity of TNF-α also exhibit enhanced activity in at least one matrix metalloproteinase. A skilled artisan would have been motivated and have had a reasonable expectation of success to use enoxaparin, a low molecular weight heparin particularly disclosed by YEDA, to treat the disorders of B.F.GOODRICH, since B.F.GOODRICH also discloses compositions comprising heparin, which only differs from a low molecular weight heparin, such as enoxaparin, in that they show improved antithrombotic performance as well as double the half-life and higher bioavailability.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Conclusion

Claims 1-10 are pending. Claims 1-8 are rejected. Claims 9-10 are withdrawn. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
March 21, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600